

# **Clinical Studies for Local Delivery of Nasal Aerosols and Sprays**

Izabela J. Roman, MD, PhD  
Founder & Medical Director  
Target Research Associates, Inc.

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Bioequivalence is assumed when  
the 90% confidence interval  
ranges between 80 - 120% for the  
target parameters (for normally  
distributed data).

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## **Three Clinical Models**

- Day(s) in the Park
- Environmental Unit
- Traditional Clinical Study

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### **Model 1 continued DAY(S) IN THE PARK STUDY**

#### Strengths

- Short duration - implications for less variability
- Cohort enrollment - less environmental variability
- More controlled compliance
- Potential for greater number of time points for subjective and objective data

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## **Model 1 continued**

### **DAY(S) IN THE PARK STUDY**

#### Weaknesses

- Restricted to seasons
- Short duration - drug may not reach max effect
- Weather risk
- Lack of site/population diversity - less representative of geography of the entire U.S.
- Susceptible to single investigator influence
- Lower variability than traditional study model
- Potential for high incidence of some AE's, e.g. sedation, since subjects often bored
- Not good for safety over time information

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## **Model 1 continued**

### **DAY(S) IN THE PARK STUDY**

#### Most Frequently Used for:

- Pilot efficacy of new drugs
- Onset of action
- Dose response
- Duration of effect for single dose

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**Model 1 continued**  
**DAY(S) IN THE PARK STUDY**

Bioequivalence Potential

Low for drugs that take  $>2$  days to  
reach maximum effect

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**Model 1 continued**  
**DAY(S) IN THE PARK STUDY**

Cost

- Up to 50 to 100 patients per treatment group
- Approx. \$2,000 per patient investigator grant

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## **Model 2 continued ENVIRONMENTAL UNIT**

### Strengths

- Same as for Day(s) in the Park model
- Controlled environment - no environmental variability
- All year round - not seasonal
- Good model for non-seasonal allergens (e.g. cat)

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## **Model 2 continued ENVIRONMENTAL UNIT**

### Weaknesses

- Farthest from reality
- Limited number of centers available
- Short duration - drug may not reach max effect
- Complex protocol - priming & establishing baseline
- Very short observation period; relevant only for a single dose study
- Safety information limited

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**Model 2 continued**  
**ENVIRONMENTAL UNIT**

Most Frequently Used for:

- Onset of action
- Pilot efficacy
- Single-dose studies

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**Model 2 continued**  
**ENVIRONMENTAL UNIT**

Bioequivalence Potential

LOW

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## **Model 2 continued ENVIRONMENTAL UNIT**

### Cost

- 30 patients per treatment group
- \$5,000 per patient investigator grant

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## **Model 3 continued TRADITIONAL CLINICAL STUDY**

### Strengths

- Closest to reality
- Availability of sites
- Well tested and validated
- Geographic diversification
- Longer duration versus other models -  
implications regarding steady state efficacy as  
well as longer term safety.

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**Model 3 continued:**  
**TRADITIONAL CLINICAL STUDY**

Weaknesses

- High variability across sites
- Greater variable within a site due to non-cohort enrollment
- Lower sensitivity
- Season dependent, unless perennial rhinitis
- Less control over compliance
- Dependence on patient diaries

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**Model 3 continued**  
**TRADITIONAL CLINICAL STUDY**

Most Frequently Used for:

- Efficacy and safety
- Dose response
- Comparative studies

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**Model 3 continued**  
**TRADITIONAL CLINICAL STUDY**

Bioequivalence Potential

HIGH - the best of all models

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**Model 3 continued**  
**TRADITIONAL CLINICAL STUDY**

Cost

- 130 - 150 patients per treatment group
- Approx. \$1,200 grant per patient

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## Improvements to Traditional Study Model

- Vehicle control rather than dose response
- No vehicle run-in period, in order to increase baseline severity and ability to discern differences in treatment groups
- Screening run-in for certain level of symptoms over days rather than only at randomization point.

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## General Problems with In-Vivo Bioequivalence Studies

### 1. Low Sensitivity

Changing Nature of Disease

Variable Environmental Conditions

Subjective Efficacy Measurements

Spray Dose Form  
(user tech. Depend.)



High Variability



Low Sensitivity

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## **General Problems with In-Vivo Bioequivalence Studies** continued

1. Limited or lack of dose response
2. Difficulty in blinding
3. Vehicle and placebo responses make it difficult to distinguish between treatments
3. Limited, gross, and non-standardized scales for efficacy measurements